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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/661,207	09/12/2003	Francis Edward Dwulet	BMID9809CUS	7205

23690 7590 08/23/2004

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EXAMINER
KOSSON, ROSANNE

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 08/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/661,207	DWULET ET AL.	
	Examiner	Art Unit	
	Rosanne Kosson	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) *10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicants' election without traverse of claims 1-9 in the reply filed on July 23, 2004 is acknowledged. Claim 10 is withdrawn from further consideration pursuant to 37 CFR 1 .142(b) as being drawn to a nonelected invention. It is suggested that the nonelected claim be canceled in response to this Office action to expedite prosecution.

Applicants' election without traverse of the species of SEQ ID NO: 1 by telephone on August 10, 2004 is also acknowledged.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 8 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claim 8 recites a method of purifying a recombinant fusion protein comprising a tag peptide by using a modified psychrophilic enzyme to which the tag peptide binds. The specification, however, does not disclose an enzyme-tag peptide substrate pair that could be used in this method. The specification states that psychrophilic enzymes may

be used, and the example of North Atlantic cod trypsin is given, but no indication is provided as to which tag peptides bind to this enzyme. Thus, the specification provides no guidance to one of skill in art for identifying or for preparing a tag peptide that may be used in this method. The claimed method is merely an invitation to further experimentation. Thus, a holding of non-enablement is required.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Claims 1 and 9 at step (c), as well as claim 8, recite "eluting" which is confusing because this term is used only in connection with passing a liquid through a solid material such as a resin to remove bound material, particularly as in chromatography. There does not appear to be a chromatographic binding step preceding this step.

Claims 1, 8 and 9 also recite a "modified enzyme," which is vague and indefinite because the nature and manner of the modification are unclear rendering the metes and bounds of the claim unclear. Is the modification, for example, a change in sequence, a chemical modification of a side chain, or substitution of an isotope?

Regarding claim 6, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP §2173.05(d).

Claims 7-8 recite the limitation "capture protein" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Altman et al. (Protein Engineering 4(5) :593-600, 1991). Altman discloses a method for purifying a recombinant fusion peptide comprising a tag peptide, in which the tag peptide portion (BPTI, a chymotrypsin inhibitor) binds to an immobilized enzyme (chymotrypsin linked to Affi-Gel). Impurities are washed from the Affi-Gel, and the fusion protein is removed and purified by washing the Affi-Gel with an acidic solution (see Abstract and p. 595, Cleavage and affinity purification). Thus, a holding of anticipation is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicants are advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Borjigin et al. (Proc Natl Acad Sci 90:337-341, 1993) in view of Altman et al. (Protein Engineering 4(5) :593-600, 1991), Roberts et al. (Proc Natl Acad Sci USA 89 :2429-2433, 1992), Maclennan et al. (US 6,326,155) and Conklin (US 6,380,354).

Borjigin discloses a method of forming fusion proteins with bovine pancreatic trypsin inhibitor (BPTI) and binding the fusion protein to biotinylated trypsin or anhydrotrypsin. The complex is then purified on an avidin-agarose bead column. Near homogeneity was obtained (see Figure 8). The BPTI-anhydrotrypsin tag system is suggested to be useful in protein purification, although BPTI derivatives with lower affinity would prove more useful when eluting from anhydrotrypsin (see p. 341, last paragraph). Borjigin does not disclose explicitly dissociating the fusion peptide from the enzyme after purifying the recombinant fusion protein.

Altman discloses forming a fusion protein with BPTI, binding the fusion protein to chymotrypsin immobilized on a solid support, cleaving and eluting the BPTI-containing

fusion protein, and, finally, purifying the BPTI portion (see Abstract and p. 595, Cleavage and affinity purification).

Roberts and Maclennan both disclose that, using phage display libraries (with M13, for example), it is possible to engineer modified affinity binding ligands based upon naturally occurring protease inhibitors with more desirable properties or either increased or decreased affinity for a target enzyme, such as human neutrophil elastase (HNE) and tissue plasminogen activator (tPA) (see Roberts, p. 2429, right column, 1st paragraph; p. 2430, Results, 1st paragraph; and pp. 2431-2432, Selection of engineered protease inhibitors with high affinity for HNE and Characterization of selected clones). The target enzyme is used to screen the libraries for binding affinity under various conditions of temperature, pH, salt concentration or % volume of an organic cosolvent. At column 13, line 54 to column 14, line 10, Maclennan discusses a number of suitable stable inhibitor domains that are suitable candidates for this engineering, including, the Kunitz domain.

Conklin (US 6,380,354) disclose that affinity tag peptides are widely used to purify or detect recombinant proteins. "In principle, any peptide or protein for which an antibody or other specific binding agent is available can be used as an affinity tag" (column 3, lines 42-44). A number of such affinity tags already in use are briefly described at column 3, lines 44-55.

A person of ordinary skill in the art at the time the invention was made would have been motivated to use the inhibitor peptide tags of Borjigin and Altman in the general process of purifying recombinant proteins because Conklin especially indicates

that any peptide with a specific binding agent can be used. The well-known procedures when the tags are other than peptide inhibitors always include steps of cleavage of the tag followed by separation of the tag and cleaving protease. The selection of a particular inhibitor-enzyme pair is an arbitrary matter of experimental design choice. Hence, it would have been prima facie obvious to one of ordinary skill in the art at the time that the invention was made to use enzyme inhibitors as affinity tags to purify recombinant proteins.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rosanne Kosson whose telephone number is 571-272-2923. The examiner can normally be reached on Monday-Friday, 8:30-6:00, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Rosanne Kosson
Examiner
Art Unit 1651

rk
2004-08-16

FRANCISCO PRATS
PRIMARY EXAMINER